HFM-48

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

D1061 B

Food and Drug Administration
Rockville MD 20857

CBER-98-011

WARNING LETTER

JAN 20 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. E. Thye Yin
Haemachem, Inc.
2335 South Hanley Road
St. Louis, MO 63144

An inspection of Haemachem, Inc., located at 2335 South Hanley Road, St. Louis, MO, was conducted from December 1 through 5, 1997. During the inspection, violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Subchapter F, Parts 600-680, and Subchapter H, Parts 809 and 820 were documented as follows:

1. Failure to notify the Director, Center for Biologics Evaluation and Research (CBER), of proposed changes in location, equipment, responsible personnel, and manufacturing methods for your product, Limusate® Limulus Amebocyte Lysate (LAL), [21 CFR 601.12] in that:

   a. modifications to the approved manufacturing process for your product have been made; these changes include

      1) reduction in the amount of [redacted] used in the [redacted] extraction of the crude lysate
      2) reduction in the amount of [redacted] added during purification of the crude lysate (b)(4)
      3) modification of pH adjustment specifications and in-process storage specifications
      4) addition, deletion, and rearrangement of process steps during purification of the crude lysate.

   b. a [redacted] was installed and is being utilized in the freeze drying of your product. (b)(4)

2. Failure to develop, conduct, control and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)] in that:

a. your stability study does not include moisture and sterility testing.

b. your standard operating procedure (SOP) entitled [redacted] is not followed in that only one potency assay has been performed on one vial of each lot of LAL in the stability study since 1991.

c. your SOP entitled [redacted] is inadequate in that the procedure does not specify the storage conditions for samples retained for testing; storage temperature data are not included in the stability test records.

d. samples from LAL lots produced in 1997 have not been included in the stability study.

e. records indicate that expiry dates have been extended beyond the currently approved product dating period of four years; data is not available to support these expiry date extensions.

3. Failure to establish and maintain procedures for control of changes to a specification, method, process or procedure [21 CFR 820.70(b)] in that there is no written procedure addressing changes made to your manufacturing process, specifications, or associated documents.

4. Failure to establish, maintain and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c)] in that:

a. non-viable particulate monitoring is not performed during filling operations.

b. the area surrounding the [redacted] laminar air flow cabinets utilized for aseptic filling of your product is not environmentally classified or controlled; viable and non-viable particulate monitoring are not performed.

c. environmental monitoring of aseptic filling personnel is not performed.

5. Failure to establish, maintain, and follow procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)] in that final product containers are not cleaned prior to depyrogenation and filling.

6. Failure to establish, maintain and follow schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met and to document such activities [21 CFR 820.70(g)] in that:

   a. sanitization records are not maintained for the [redacted] lyophilizer utilized in the freeze drying of your product.

   b. silicon tubing utilized in filling your product is depyrogenated and reused [redacted] number of times; your SOP entitled [redacted] [redacted] does not address cleaning, depyrogentation, or replacement of the silicon tubing. (b)(4)

7. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75] in that:

   a. aseptic media fills have not been performed to validate your filling process.

   b. revalidation was not performed following changes to your approved manufacturing process including modification of in-process specifications and addition, deletion, and rearrangement of manufacturing steps.

   c. data are not available to support the effectiveness of storage of finished product, raw materials, and crude lysate in the [redacted] walk-in freezer.

8. Failure to maintain a device master record (DMR) which includes, or refers to the location of, production process specifications including appropriate equipment specifications, production methods, production procedures, and production environment specifications [21 CFR 820.181]. Your DMR describes in-process storage specifications as "a couple of days", "a few days" and "up to 10 days" instead of defining formal limits for in-process storage specifications.

9. Failure to maintain device history records (DHRs) for each batch, lot, or unit to demonstrate that the product is manufactured in accordance with the device master record (DMR) [21 CFR 820.184] in that:

   a. device history records (DHRs) are not always completed during actual production. Operators use notebook paper to record data obtained during performance of manufacturing steps; DHRs are completed at a later date and time. Notes used to complete DHRs are not always maintained [21 CFR 600.12].

b. device history records for LAL lots # 039601, #049602, #069607, #119606, and #119602 were not maintained.

c. although in-process storage specifications in the DMR describes storage as "up to 10 days" during purification of the crude lysate, records indicate extracted lysate was stored from March 15, 1997 to April 2, 1997 during production of lot #019705.

10. Failure to establish, maintain, and follow procedures to control all documents including procedures providing for document approval, distribution and changes [21 CFR 820.40(b)] in that: (b)(4)

a. your SOPs entitled [~~~~~] lack documentation of approval, including the date and signature of the individual(s) approving the documents.

b. records of modifications to your approved manufacturing process and the related device history record, including modification of in-process specifications and addition, deletion, and rearrangement of manufacturing steps, were not maintained.

11. Failure to establish, maintain and follow procedures to ensure that specified requirements for in-process products and acceptance criteria for finished devices are met [21 CFR 820.80] in that your SOP entitled [~~~~~] [~~~] is not being followed; portions of incubated samples exhibiting turbidity on the third or fourth day of incubation are not being transferred to fresh medium as specified by your SOP and as required by 21 CFR 610.12. (b)(4)

11. Failure to establish and maintain procedures to ensure that all purchased or otherwise received products and services conform to specified requirements [21 CFR 820.50] in that your SOP entitled [~~~~~] does not describe the quality requirements for raw materials received including [~~~] [~~~~~] (b)(4)

13. Failure to establish, maintain and follow procedures to control labeling activities and to store labeling in a manner that provides proper identification and is designed to prevent mixups [21 CFR 820.120] in that:

a. vial labels printed with the same potency levels but different lot numbers were stored immediately adjacent to one another.

b. blank package labels for 1 mL and 5 mL kit configurations are stored without any segregation.

c. German versions of preprinted and blank vial and package labels are stored without any segregation.

d. your SOP entitled [redacted] is not followed; vial and package labels were observed being stored in an unlocked cabinet.

e. your SOPs entitled [redacted] and [redacted] are not followed; labeling receipt, tracking and usage records have not been maintained since July 1995.

14. Failure to establish, maintain and follow procedures for implementing corrective and preventative action including requirements for investigating the cause of nonconforming product and identifying the action(s) needed to correct and prevent recurrence of nonconformities and other quality problems [21 CFR 820.100] in that there is no written procedure addressing investigation, correction, and prevention of deviations relating to product processes, specifications and equipment.

15. Failure to establish and maintain procedures for receiving, reviewing and evaluating complaints by a formally designated unit [21 CFR 820.198] in that there is no written procedure addressing complaint handling.

The above violations are not intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility as management to assure that your establishment is in compliance with all requirements of the federal regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction, and/or civil penalties.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. All corrective actions will be verified during reinspection of your facility.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

Sincerely,

for,

James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research